

## REMARKS

Claims 1-15 are pending. Claims 1-15 stand rejected. Claim 1 is amended. Support is found in the specification and claims as filed.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

### **35 U.S.C. § 103(a) rejection**

*A. Powell in view of D'Amato, Kawai and Powell II*

Claims 1, 4-9, and 13-15 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Powell et al. U.S. Patent No. 3,793,454 ("Powell") in view of D'Amato et al. U.S. Patent No. 5,712,291 ("D'Amato") and Kawai et al., Cancer Lett. 2001 Oct. 10; 171(2):201-07 ("Kawai"), and in further view of Powell et al., J. Pharmaceutical Sciences. August 1972 61(8):1227-1230 (hereinafter "Powell II").

Powell et al. discloses the use of harringtonine and isoharringtonine to treat L1210 and P388 leukemia tumors. Powell et al. fails to teach that each leukemia strain is an angiogenic disease and is not a solid tumor.

D'Amato asserts that angiogenesis is associated with blood-born tumors such as leukemias and that it plays a role in the abnormalities in the bone marrow that give rise to leukemic-like tumors.

Kawai et al. teaches that leukemic cell lines are representative of non-solid tumors.

However, as noted by the Examiner, "[w]hile ... the prior art is silent with respect to the inhibition of angiogenesis, the claims are nevertheless believed to remain properly rejected because...angiogenesis and the claimed diseases/disorders have been associated. Thus, inherent in the prior art is what Applicant is claiming." (see p. 4 of the October 5, 2007 Office Action) Applicants respectfully traverse.

The Examiner's position appears to be that administration of the compounds of Powell to mice harboring tumors inherently discloses a method of inhibiting angiogenesis in a host with an angiogenic disease. As noted in previous responses, the method of Powell that includes the use

of leukemia cell suspensions in the peritoneal cavity, do not form solid tumors that require vascularization, as is known in the art. This being the case, the combined teachings of the cited art would not lead the skilled artisan to the conclusion that (1) the injection of harringtonine and isoharringtonine in the peritoneal cavity to treat suspended L1210 and P388 cells would result in an anti-angiogenic effect; and (2) that harringtonine and isoharringtonine would have any effect on a solid tumor that requires vascularization. It was the inventor, not the prior art, who discovered the anti-angiogenic property of cephalotaxines.

Applicants are aware that the present rejection is based on obviousness, not anticipation. However, the MPEP makes clear that inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." (see MPEP 2112, citing *In re Napier*, 55 F.3d 610, 613.) Thus, the law regarding the propriety of a rejection under 102 is applicable to rejections under 103. In this regard, Applicants note that the law regarding inherency is established such that where the reference is silent as to a specific limitation in the claims (e.g. inhibiting angiogenesis), such a gap in the reference must be filled with recourse to extrinsic evidence in order for the reference to serve as an anticipatory reference by inherency. Such evidence must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, *and that it would be so recognized by persons of ordinary skill in the art.* Continental Can Co. USA, Inc. v. Monsanto Co., 20 USPQ2d 1746, 1749-1750 (Fed. Cir. 1991). The characteristic must flow undeniably and irrefutably from the express disclosures of the prior art reference. Mere possibilities or even probabilities are not enough to support a finding of anticipation. Motorola, Inc. v. Interdigital Technology Corp., 43 USPQ2d 1481 (Fed. Cir. 1997). In relying upon a theory of inherency, the Office Action must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art. Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd.Pat.App.& Inf. 1990).

It has also been held that an unexpected, accidental result, occurring along with a known and expected one, cannot anticipate a claimed invention. For example, in In re Marshall the claims were directed toward the use of a drug to inhibit the release of certain hormones in order to control weight gain where the drug had a known use for treatment of esophagitis, gastritis,

peptic ulcer, and irritable colon syndrome. 198 USPQ 344 (CCPA 1978). Holding that the prior art teaching did not anticipate appellant's process claims, the court noted that "[n]othing in the [reference] remotely suggests taking oxethazaine to lose weight. If anyone ever lost weight by following the [reference] teachings it was an unrecognized accident. An accidental or unwitting duplication of an invention cannot constitute an anticipation." *Id.* at 346.

Likewise, if administration of Powell's compounds to tumor bearing mice resulted in inhibition of angiogenesis, at best, this should be considered an accidental or unwitting duplication of an invention and therefore cannot constitute anticipation (or a basis of obviousness). Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

B. Chinery in view of D'Amato, Cecil's, O'Dwyer, and Medford

Claims 1-15 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chinery et al. U.S. Application No. 2001/0049349 ("Chinery") in view of D'Amato et al. U.S. Patent No. 5,712,291 ("D'Amato"), Cecil's Textbook of Medicine, pp. 1060-1074 ("Cecil's"), O'Dwyer et al., J. Clin. Oncol., 4:10(October), 1986, pp. 1563-1568 ("O'Dwyer") and Medford et al. U.S. Patent No. 5,380,747 ("Medford"), and in further view of Powell II. Applicants respectfully disagree.

Chinery is the primary reference and discloses the use of antineoplastic agents in combination with antioxidants to treat hyperproliferative conditions.

Again, the Examiner notes that an inherent property of the prior art renders the claims obvious. However, as noted previously, the characteristic in question must flow undeniably and irrefutably from the express disclosures of the prior art reference. Mere possibilities or even probabilities are not enough to support a finding of anticipation. Motorola, Inc. v. Interdigital Technology Corp., 43 USPQ2d 1481 (Fed. Cir. 1997). In relying upon a theory of inherency, the Office Action must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art. Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd.Pat.App.& Inf. 1990). In addition, it has also been held that an unexpected, accidental result, occurring along with a

known and expected one, cannot anticipate a claimed invention. That is, an accidental or unwitting duplication of an invention cannot constitute an anticipation.” In re Marshall, at 346.

Moreover, Applicants note that “[t]he discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using.” (see MPEP 2112.02, citing *In re Hack*, 245 F.2d 246, 248.) Here, the new use is the inhibition of angiogenesis. Prior to Applicants invention, it was not appreciated that cephalotaxine could be used in a method of inhibiting angiogenesis or a method of inhibiting the onset or progression of an angiogenic disease in a host. Thus, the new use is patentable.

In addition, Applicants note that “[o]bviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established.” (see MPEP 2141.02(V), citing *In re Rijckaert*, 9 F.2d 1531.) Again, the anti-angiogenic effect of cephalotaxine was not known prior to Applicants invention. Even assuming, *arguendo*, that the anti-angiogenic property of cephalotaxine was present in Powell II, Applicants submit that the later establishment of this property should not preclude patentability of a method of inhibiting angiogenesis. Because the suggestion to combine or modify references must occur prior to an Applicant’s invention, an unknown inherency cannot supply this suggestion at the required time. “Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection.” (*Id.* citing *In re Newell*, 891 F.2d 899, 901.) As such, Applicants submit that they fail to provide the requisite motivation for their combination. In view of this, Applicants respectfully request the Examiner to withdraw the rejection.

### **Double Patenting Rejections**

Claims 1- 15 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over either of claims 1, 17 and 19-24 of co-pending 10/769,638 or claims 7, 8 and 13-15 of copending Application No. 10/631,106.

Claim 1 of co-pending Application No. 10/769, 638 claims a method of treatment of a host with a cellular proliferative disease comprising contacting the host with homoharringtonine and camptothecin each in an amount to modulate the cellular proliferative disease.

Claim 15 of co-pending application No. 10/631, 106 is directed to a method of treating a host with a cellular proliferative disease comprising contacting the host with amonafide in conjunction with homoharringtonine each in an amount sufficient to have an anticancer effect on said cellular proliferative disease, wherein the cellular proliferative disease is a solid tumor.

As noted previously, the law regarding inherency is established such that where the reference, or in this case the claims of a patent application, is/are silent as to a specific limitation in the claims (e.g. inhibiting angiogenesis), such a gap must be filled with recourse to extrinsic evidence in order for the reference to serve as an anticipatory reference by inherency. The characteristic must flow undeniably and irrefutably from the express disclosures of the prior art reference. Here, Applicants note that the claims in the cited applications are silent with respect to inhibition of angiogenesis or inhibiting the onset or progression of an angiogenic disease by inhibiting angiogenesis. While possible, it is not necessarily an inherent property of the claims of the cited applications that angiogenesis is inhibited. Based upon the foregoing, it is submitted that the double patenting rejections based on an alleged inherent property of the claims of the cited applications should be withdrawn.

### CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 442-1255.

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